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Sheet 1 of 1

Complete if Known	
Application Number	10/698,924
Filing Date	October 31, 2003
First Named Inventor	K. Raja Reddy
Art Unit	1626
Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if Known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
TO	AD	3,018,302	01/23/1962	Bielefeld *et al.*	
	AE	3,116,282	12/31/1963	Hunter	
	AF	4,440,740	04/03/1984	Fix *et al.*	
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	AI	6,752,981	06/22/2004	Erion *et al.*	
	AJ	2003/0229225 A1	12/11/2003	Reddy *et al.*	
	AK	2003/0225277 A1	12/04/2003	Kopcho *et al.*	
	AL	2004/0092476 A1	05/13/2004	Erion *et al.*	
	AM	2005/0288240 A1	12/29/2005	Erion *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
TO	AN	EP 0161955 A1	11/21/1985	Merck & Co., Inc.		
	AO	EP 0180276 A1	05/07/1986	Oce-Andeno B.V.		
	AP	EP 0338372 A2	10/25/1989	American Cyanamid Co.		
	AQ	EP 0353692 B1	10/04/1995	Nissan Chemical Ind., Ltd.		
	AR	EP 0481214 B1	06/24/1998	Inst. Organic Chem. & Biochem. Acad. Sci. Czech. Repub. X		
	AS	WO 91/19721 A1	12/26/1991	Glazier		
	AT	WO 96/01267 A1	01/18/1996	Takeda Chemical Ind., Ltd.		
	AU	WO 97/03679 A1	02/06/1997	Cephalon, Inc.		
	AV	WO 00/52015 A2	09/08/2000	Metabasis Therapeutics, Inc.		

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Examiner Signature	T. A. Solola	Date Considered	1-31-06

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Attorney Docket Number	2358.0180003/RWE/AES

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published	T[2]
YO	AW	ALEXANDER, P., *et al.*, "Preparation of 9-(2-Phosphonomethoxyethyl) Adenine Esters as Potential Prodrugs," *Collect. Czech. Chem. Commun.* 59:1853-1869, Czech Academy of Sciences, Institute of Organic Chemistry and Biochemistry (1994) ✓	
	AX	AMIN, D., *et al.*, "1-Hydroxy-3-(methylpentylamino)-propylidene-1,1-bisphosphonic Acid as a Potent Inhibitor of Squalene Synthase," *Arzneim.-Forsch/Drug Res. 46*:759-762, Blackwell Publishing, Inc. (1996) ✓	
	AY	ARNÉR, E.S.J. and ERIKSSON, S., "Mammalian Deoxyribonuleoside Kinases," *Pharmacol. Ther. 67*:155-186, Elsevier Science Ltd. (1995) ✓	
	AZ	ATIQ, O., *et al.*, "Treatment of Unresectable Primary Liver Cancer with Intrahepatic Fluorodeoxyuridine and Mitomycin C Through an Implantable Pump," *Cancer 69*:920-924, John Wiley and Sons, Inc. (1992) ✓	
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	BB	BALTHAZOR, T. and Grabiak, R.C., "Nickel-Catalyzed Arbuzov Reaction: Mechanistic Observations," *J. Org. Chem. 45*:5425-5426, American Chemical Society (1980) ✓	
	BC	BEAUCAGE, S.L. and Iyer, R.P., "The Synthesis of Modified Oligonucleotides by the Phosphoramidite Approach and Their Applications," *Tetrahedron 49*:6123-6194, Pergamon Press Ltd. (1993) ✓	
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	BE	BIRD, J., *et al.*, "Synthesis of Novel *N*-Phosphonoalkyl Dipeptide Inhibitors of Human Collagenase," *J. Med. Chem. 37*:158-169, American Chemical Society (1994) ✓	
	BF	BORCH, R.F. and Millard, J.A., "The Mechanism of Activation of 4-Hydroxycyclophosphamide," *J. Med. Chem. 30*:427-431, American Chemical Society (1987)	

Examiner Signature	T. A. Solola	Date Considered	1-31-06

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YO	BG	BRILL, T. and Landon, S.J., "Arbuzov-like Dealkylation Reactions of Transition-Metal-Phosphite Complexes," *Chem. Rev. 84*:577-585, American Chemical Society (1984)	
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	BO	DEARFIELD, K., *et al.*, "Analysis of the genotoxicity of nine acrylate/methacrylate compounds in L5178Y mouse lymphoma cells," *Mutagenesis 4*:381-393, Oxford University Press (1989)	
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First Named Inventor	K. Raja Reddy
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Yo	BR	DE LOMBAERT, S., *et al.*, "*N*-Phosphonomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors," *J. Med. Chem. 37*:498-511, American Chemical Society (1994)	
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	BV	ENRIQUEZ, P., *et al.*, "Conjugation of Adenine Arabinoside 5'-Monophosphate to Arabinogalactan: Synthesis, Characterization, and Antiviral Activity," *Bioconjugate Chem. 6*:195-202, American Chemical Society (1995)	
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	BZ	ERION, M., "Liver-Targeted Nucleoside Prodrugs," presented at the *Gordon Research Conference: Purines, Pyrimidines and Related Substances*, Newport, RI, 38 pages (June-July 2003)	
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	CB	FARQUHAR, D., *et al.*, "Biologically Reversible Phosphate-Protective Groups," *J. Pharm. Sci.* 72:324-325, American Chemical Society (1983)	

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Sheet 4 of 10

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First Named Inventor	K. Raja Reddy
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Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

Yo	CC	FARQUHAR, D., *et al.*, "Synthesis and Antitumor Evaluation of Bis[(pivaloyloxy) methyl] 2'-Deoxy-5-fluorouridine 5'-Monophosphate (FdUMP): A Strategy to Introduce Nucleotides into Cells," *J. Med. Chem.* 37:3902-3909, American Chemical Society (1994)	
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	CL	HE, K., *et al.*, "Inactivation of Cytochrome P450 3A4 by Bergamottin, a Component of Grapefruit Juice," *Chem. Res. Toxicol.* 11:252-259, American Chemical Society (1998)	
V	CM	HESSLER, "An Efficient Synthesis of 1-ß-D-Arabinofuranosylcytosine," *J. Org. Chem.* 41:1828-1831 (1976)	

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First Named Inventor	K. Raja Reddy
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Y0	CN	HILLERS, S., *et al.*, "Analogs of pyrimidinemono-and polynucleotides. VI. Phosphates of 1-(1,4-dihydroxy-2-pentyl)thymine and 1-(1,3-dihydroxy-2-propyl) uracil," *Chemical Abstracts* 89(17), Chemical Abstracts Service (1978)	
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	CW	LEFEBVRE, I., *et al.*, "Mononucleoside Phosphotriester Derivatives with *S*-Acyl-2-thioethyl Bioreversible Phosphate-Protecting Groups: Intracellular Delivery of 3'-Azido-2',3'-dideoxythymidine 5'-Monophosphate," *J. Med. Chem.* 38:3941-3950, American Chemical Society (1995)	
↓	CX	LOK, A.S.F., *et al.*, "Neurotoxicity associated with adenine arabinoside monophosphate in the treatment of chronic hepatitis B virus infection," *J. Antimicrob. Chemotherap.* 14:93-99, Oxford University Press (1984)	

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YO	CY	LU, X. and Zhu, J., "Palladium-Catalyzed Reaction of Aryl Polyfluoroalkanesulfonates with O,O-Dialkyl Phosphonates," *Synthesis (8)*:726-727, Georg Thieme Verlag (1987)	
	CZ	LUDEMAN, S.M., *et al.*, "Synthesis and Antitumor Activity of Cyclophosphamide Analogues. 4. Preparation, Kinetic Studies, and Anticancer Screening of "Phenylketophosphamide" and Similar Compounds Related to the Cyclophosphamide Metabolite Aldophosphamide," *J. Med. Chem. 29*:716-727, American Chemical Society (1986)	
	DA	MACKENNA, D., *et al.*, "MB07133: A HepDirect™ Prodrug of Cytarabine Monophosphate for Use in Hepatocellular Carcinoma," *Heptaology 38(Suppl. 1)*:411A, AASLD Abstract No. 524, John Wiley & Sons, Inc. (October 2003)	
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	DF	MELVIN, L.S., "An Efficient Synthesis of 2-Hydroxyphenylphosphonates" *Tetrahedron Lett.* 22:3375-3376, Pergamon Press Ltd. (1981)	
	DG	MEYER, R., *et al.*, "2'-O-Acyl-6-thioinosine Cyclic 3',5'-Phosphates as Prodrugs of Thioinosinic Acid," *J. Med. Chem. 22*:811-815, American Chemical Society (1979)	
	DH	MITCHELL, A., *et al.*, "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Phosphoesters of Methylphosphonate and Phosphonacetate," *J. Chem. Soc. Perkin Trans. 1*, 2345-2353, Royal Society of Chemistry (1992)	
	DI	MITSUNOBU, O., "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products," *Synthesis (1)*:1-28, Georg Thieme Verlag (1981)	

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Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

Y.O	DJ	MONTAG, A., *et al.*, "The Effect of Dexamethasone Treatment on CYP3A Activity Distribution, the Liver Targeting of MB07133 and CYP3A Activity in a Highly Proliferating State in Rats," *Hepatology 40(Suppl. 1)*:649A, AASLD Abstract No. 1123, John Wiley & Sons, Inc. (2004)	
	DK	MOORE, M., *et al.*, "Comparison of mutagenicity results for nine compounds evaluated at the *hgprt* locus in the standard and suspension CHO assays," *Mutagenesis 6*:77-85, Oxford University Press (1991)	
	DL	MURRAY, G., *et al.*, "Cytochrome P450 CYP3A in human renal cell cancer," *Brit. J. Cancer 79*:1836-1842, Nature Publishing Group (1999)	
	DM	MURRAY, G., *et al.*, "Cytochrome P450 Expression Is a Common Molecular Event in Soft Tissue Sarcomas," *J. Pathology 171*:49-52, John Wiley & Sons, Ltd. (1993)	
	DN	NAKAYAMA, K. and Thompson, W.J., "A Highly Enantioselective Synthesis of Phosphate Triesters," *J. Am. Chem. Soc. 112*:6936-6942, American Chemical Society (1990)	
	DO	NEIDLEIN, R., *et al.*, "Mild Preparation of 1-Benzyloxyiminoalkylphosphonic Dichlorides: Application to the Synthesis of Cyclic Phosphonic Deisters and Cyclic Monoester Amides," *Heterocycles 35*:1185-1203, Elsevier Science (1993)	
	DP	NIFANTYEV, E.E., *et al.*, "Synthesis and Structure of Some Stable Phospholane-Phospholanes," *Phosphorus, Sulfur and Silicon 113*:1-13, Overseas Publishers Association (1996)	
	DQ	OGG, M., *et al.*, "A reporter gene assay to assess the molecular mechanisms of xenobiotic-dependent induction of the human CYP3A4 gene *in vitro*," *Xenobiotica 29*:269-279, Taylor & Francis Ltd. (1999)	
	DR	OHASHI, K., *et al.*, "Synthesis of Phosphonosphingoglycolipid Found in Marine Snail Turbo Comutus," *Tetrahedron Lett. 29*:1189-1192, Pergamon Press plc (1988)	
	DS	PETRAKIS, K. and Nagabhushan, T.L., "Palladium-Catalyzed Substitutions of Triflates Derived from Tyrosine-Containing Peptides and Simpler Hydroxyarenes Forming 4-(Diethoxyphosphinyl)phenylalanines and Diethyl Arylphosphonates," *J. Am. Chem. Soc. 109*:2831-2833, American Chemical Society (1987)	
↓	DT	PITCHER, H.R., "Built-in Bypass," *Nature 429*:39, Nature Publishing Group (May 2004)	

Examiner Signature	T. A. Solola	Date Considered	1-31-06

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SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 8 of 10

Complete if Known	
Application Number	10/698,924
Filing Date	October 31, 2003
First Named Inventor	K. Raja Reddy
Art Unit	1626
Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

YD	DU	PREDVODITELEV, D.A., *et al.*, "Glycero-2-Hydroxymethylene Phosphates," *J. Org. Chem. USSR, A Translation of Zhur. Org. Khim. 13*:1489-1492, Plenum Publishing Corporation (1977)	
	DV	PREDVODITELEV, D.A., *et al.*, "Synthesis of Lipids and Their Models on the Basis of Glycerol Alkylene Phosphites. V. Cyclic Phosphatidylglycerol and Phosphatidylhydroxyhomocholine," *J. Org. Chem. USSR, A Translation of Zhur. Org. Khim. 17*:1156-1165, Plenum Publishing Corporation (1981)	
	DW	REDDY, K.R., *et al.*, "Stereoselective synthesis of nucleoside monophosphate HepDirect™ prodrugs," *Tetrahedron Lett. 46*:4321-4324, Elsevier Ltd. (2005)	
	DX	REDDY, M.R., *et al.*, "Development of a Quantum Mechanics-Based Free-Energy Perturbation Method: Use in the Calculation of Relative Solvation Free Energies," *J. Am. Chem. Soc. 126*:6224-6225, American Chemical Society (published online April 2004)	
	DY	REDMORE, D., "Phosphorus Derivatives of Nitrogen Heterocycles. 2. Pyridinophosphonic Acid Derivatives," *J. Org. Chem. 35*:4114-4117, American Chemical Society (1970)	
	DZ	RUIZ VAN HAPEREN, V.W.T., *et al.*, "Induction of Resistance to 2'-2'-Difluorodeoxycytidine in the Human Ovarian Cancer Cell Line A2780," *Semin. Oncol. 22 (Suppl. 11)*:35-41, W.B. Saunders Company (1995)	
	EA	SHAW, J.-P. and Cundy, K.C., "Biological Screens of PMEA Prodrugs," *Pharm. Res. 10*:S-294, Kluwer Academic Publishers B.V., Abstract No. PDD 7480 (1993)	
	EB	SHEN, T.Y., *et al.*, "Nucleosides I. A New Synthesis of 1-β-D-Arabinofuranosyl Pyrimidine Nucleosides," *J. Org. Chem.* 30:835-838, American Chemical Society (1965)	
	EC	SHIH, Y.-E., *et al.*, "Preparation and Structures of 2-Dimethylamino-4-phenyl-1,3,2-dioxaphosphorinane-2-oxides," *Bull. Inst. Chem. Acad. Sin. 41*:9-16, Academia Sinica, Nankang, Taipei, Taiwan (1994)	
	ED	SHIRAI, R., *et al.*, "Asymmetric Synthesis of Antimitotic Combretadioxolane with Potent Antitumor Activity Against Multi-Drug Resistant Cells," *Bioorg. Med. Chem. Lett.* 8:1997-2000, Elsevier Science Ltd. (1998)	
	EE	STARRETT, Jr., J.E., *et al.*, "Synthesis, Oral Bioavailability Determination, and *in Vitro* Evaluation of Prodrugs of the Antiviral Agent 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA)," *J. Med. Chem.* 37:1857-1864, American Chemical Society (1994)	

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Sheet 9 of 10

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First Named Inventor	K. Raja Reddy
Art Unit	1626
Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

Y0	EF	THOMSON, W., *et al.*, "Synthesis, Bioactivation and Anti-HIV Activity of the Bis(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Esters of the 5'-monophosphate of AZT," *J. Chem. Soc. Perk. Trans. 1*,1239-1245, Royal Society of Chemistry (1993)	
	EG	VALENTINE, Jr., D., "Preparation of the Enantiomers of Compounds Containing Chiral Phosphorus Centers," *Asymmetric Synthesis* 4:263-312, Academic Press, Inc. (1984)	
	EH	VENOOK, A., "Treatment of Hepatocellular Carcinoma: Too Many Options?," *J. Clin. Oncol. 12*:1323-1334, American Society of Clinical Oncology (1994)	
	EI	VO-QUANG, Y., *et al.*, "(1-Amino-2-propenyl)phosphonic Acid, an Inhibitor of Alanine Racemase and D-Alanine:D-Alanine Ligase," *J. Med. Chem. 29*:579-581, American Chemical Society (1986)	
	EJ	WAGNER, A., *et al.*, "Direct Conversion of Tetrahydropyranylated Alcohols to the Corresponding Bromides," *Tetrahedron Lett. 30*:557-558, Pergamon Press plc (1989)	
	EK	WALLACE, E.M., *et al.*, "Design and Synthesis of Potent, Selective Inhibitors of Endothelin-Converting Enzyme," *J. Med. Chem. 41*:1513-1523, American Chemical Society (1998)	
	EL	WALSH, E., *et al.*, "Phenoxymethylphosphonic Acids and Phosphonic Acid Ion-exchange Resins," *Phenoxymethylphosphonic Acid Ion-Exchange Resins 78*:4455-4458, American Chemical Society (1956)	
	EM	WATKINS, P., "Noninvasive tests of CYP3A enzymes," *Pharmacogenetics* 4:171-184, Lippincott Williams & Wilkins (1994)	
	EN	WEBER, G.F. and Waxman, D.J., "Activation of the Anti-cancer Drug Ifosphamide by Rat Liver Microsomal P450 Enzymes," *Biochem. Pharm. 45*:1685-1694, Pergamon Press Ltd. (1993)	
	EO	WECHTER, W.J., *et al.*, "Nucleic Acids. 16. Orally Active Derivatives of *ara*-Cytidine[1,2]," *J. Med. Chem. 19*:1013-1017, American Chemical Society (1976)	
	EP	WEIBEL, M., *et al.*, "Potentiating Effect of {2-[2-[(2-Amino-1,6-Dihydro-6-Oxo-9H-Purin-9-yl)Methyl]-Phenyl] Ethenyl}-Phosphonic Acid (MDL 74,428), A Potent Inhibitor of Purine Nucleoside Phosphorylase, on the Antiretroviral Activities of 2',3'-Dideoxyinosine Combined to Ribavirin in Mice," *Biochem. Pharmacol. 48*:245-252, Elsevier Science Ltd. (1994)	

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Art Unit	1626
Examiner Name	Taofiq A. Solola
Attorney Docket Number	2358.0180003/RWE/AES

YD	EQ	WILEMAN, T., *et al.*, "Receptor-mediated endocytosis," *Biochem. J. 232*:1-14, Portland Press (1985)	
	ER	YU, L. J., *et al.*, "In vivo Modulation of Alternative Pathways of P-450-Catalyzed Cyclophosphamide Metabolism: Impact on Pharmacokinetics and Antitumor Activity," *J. Pharmacol. Exp. Ther. 288*:928-937, The American Society for Pharmacology and Experimental Therapeutics (1999)	
	ES	ZON, G., "Cyclophosphamide Analogues" in *Progress in Medicinal Chemistry*, Ellis, G.P., *et al.*, eds., Elsevier Biomedical Press, Chapter 4, pp. 205-246 (1982)	
	ET	ZON, G., *et al.*, "NMR Spectroscopic Studies of Intermediary Metabolites of Cyclophosphamide. A Comprehensive Kinetic Analysis of the Interconversion of *cis*-and *trans*-4-Hydroxycyclophosphamide with Aldophosphamide and the Concomitant Partitioning of Aldophosphamide between Irreversible Fragmentation and Reversible Conjugation Pathways," *J. Med. Chem. 27*:466-485, American Chemical Society (1984)	
	EU	~~International Search Report for related International Application No. PCT/US03/34709, European Patent Office, Netherlands, mailed May 11, 2004~~ Not a prior art	
	EV	~~Copy of Office Action for Co-pending United States Application No. 10/698,928, Boyer, S., *et al.*, filed October 31, 2003, mailed July 5, 2005~~ Not a prior art	

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